[JOINT CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A., AND THE INSTITUTO DE QUÍMICA DE LA UNIVERSIDAD NACIONAL AUTÓNOMA DE MÉXICO]

STEROIDS. IX. THE DIENONE-PHENOL REARRANGEMENT IN THE CHOLESTEROL SERIES

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Received April 8, 1950

Woodward and Singh (1) on the basis of model experiments in the naphthalene series have clearly demonstrated that the acid-catalyzed rearrangement of steroidal 1,4-dien-3-ones (I), first studied by Inhoffen and collaborators (2), does *not* result in the formation of 1-methyl phenols (II) as believed originally (2), but in products of unknown constitution.

In the preceding paper of this series (3), it was demonstrated that the *authentic* 1-methyl-3-hydroxy steroids (II) can be obtained by dienone-phenol rearrangement of a 1,4,6-trien-3-one (IV) followed by hydrogenation of the resulting 6-dehydro-1-methylphenol (V). Our initial study was limited to the androstane series (IV, R = O, OH) and resulted in the first synthesis of authentic, estrogenically potent, 1-methylestrone and 1-methylestradiol (II, R = O, OH; R'_4 = H).

Since Inhoffen (2) had described the synthesis of a "sterinphenol" by dienone-phenol rearrangement of 1,4-cholestadien-3-one (I, R = C_8H_{17}) and had assigned to it structure II (R = C_8H_{17}), now known to be incorrect (1, 3), it was deemed necessary to prepare the authentic aromatic cholesterol derivative by the procedure which had proved successful in our hands in the androstane series (3).

1,4,6-Cholestatrien-3-one (IV, R = C_8H_{17}), the required starting material, was previously obtained (4) as crystals with m.p. 82–83°, u.v. maxima at 224, 256, and 300 mμ, by dibromination of Δ^4-cholesten-3-one and dehydrobromination. Martens (5) has attempted to prepare this substance by Wohl-Ziegler bromination of 1,4-cholestadien-3-one (I, R = C_8H_{17}) and subsequent collidine treatment of the 6-bromo derivative III; however the trienone IV was obtained only as an oil, characterized by an impure semicarbazone. Repetition of this sequence of reactions in our laboratory gave the 6-bromo compound III, identical with that described by Martens (5), and dehydrobromination smoothly afforded the crystalline 1,4,6-cholestatrien-3-one (IV, R = C_8H_{17}) identical in all respects with the specimen prepared by the alternate procedure (4). Dienone-phenol rearrangement of this trienone in the customary manner afforded a phenolic acetate (Vb), m.p. 114°, $[\alpha]_D^{20}$ −99.6°, which on saponification led to the free 6-dehydro-1-methyl phenol (Va), m.p. 146°, $[\alpha]_D^{20}$ −131°, u.v. maxima (Fig. 1) at 228, 266, and 304 mμ, and on methylation to the methyl ether Vc. The phenol V thus exhibited the typical negative rotation of 6-dehydrophenols (6) and the characteristic ultraviolet absorption spectrum of a phenol with an additional double bond in the *meta* position (3, 4, 7). Catalytic hydrogenation of the acetate Vb and saponification produced 1-methyl-3-hydroxy-19-nor-1,3,5-cholestatriene (IIa) with m.p. 128°, $[\alpha]_D^{20}$ + 135° and a characteristic phenolic spectrum shown in Fig. 1. As observed already in several instances (3, 4), hydro-

genation of the 6,7 double bond results in a large increase in the rotation and in a bathochromic shift of the main ultraviolet maximum (at 268 mμ) with concomitant lowering of the extinction coefficient. This 1-methyl phenol (II, R = C_8H_{17}) differed completely in its properties from those of the so-called "sterinphenol," to which has previously been assigned (2) the constitution II, and which possesses m.p. 145–146° (2, 8), $[\alpha]_D^{20}$ +161° (8). Inhoffen's "sterinphenol" should therefore also be classed among the "x-methyl*hetero*phenols" (*cf.* 3).

Dehydrogenation of the 6-dehydro acetate Vb with selenium dioxide in acetic acid solution yielded the naphthalenic analog, 1-methyl-3-hydroxy-19-nor-1,3,5,6,8-cholestapentaene (VIa), which rapidly decomposed on exposure to light and air. Aside from tetradehydroneoergosterol (9), VIa appears to be the

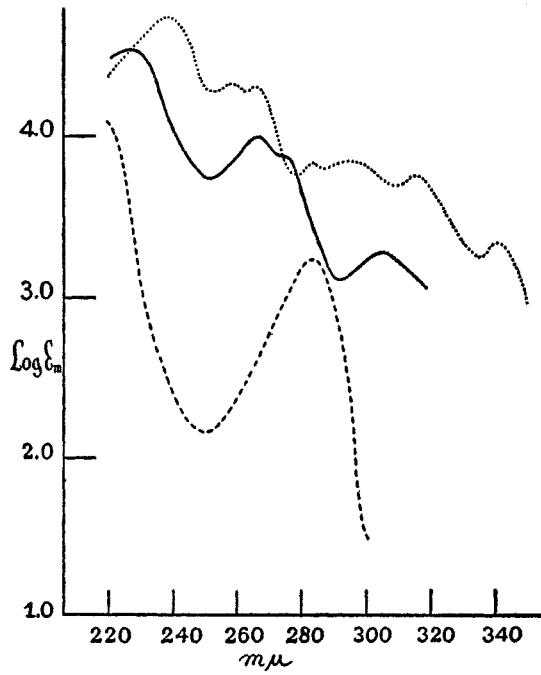


FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA (in 95% ethanol solution): Va, ——; IIa, – – –; VIa, ...

only naphthalenic sterol (hydrocarbon side chain) known. In contrast to the corresponding androstane derivatives (II, V, VI, R = O, OH), the presently described phenols of the cholesterol series are only very slightly soluble in aqueous alkali; they give no color with alcoholic ferric chloride solution.

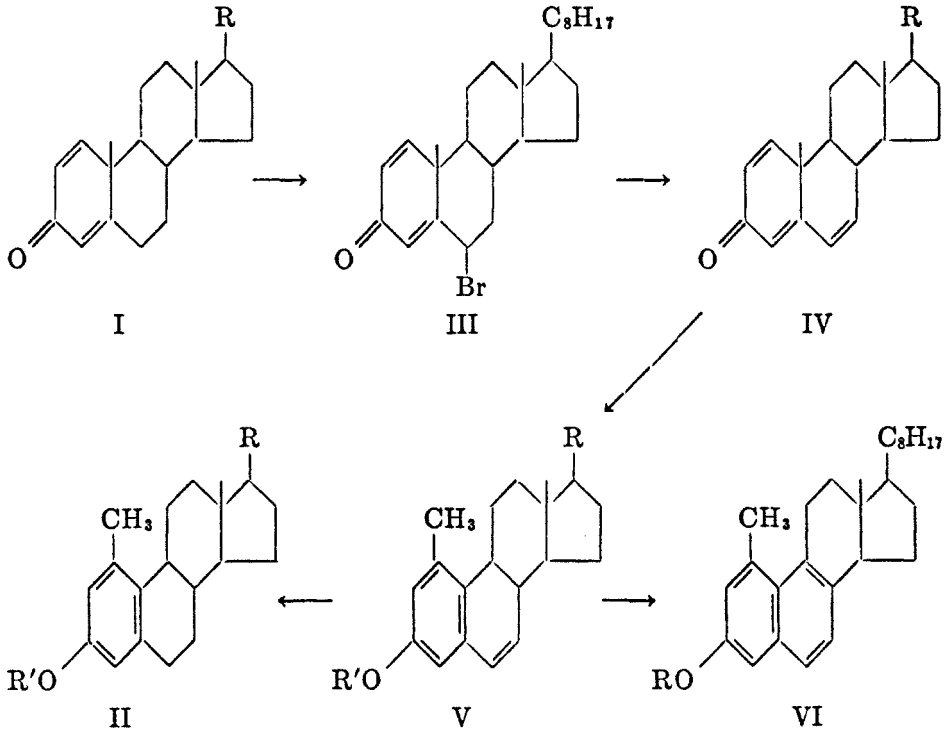
EXPERIMENTAL[1]

6-Bromo-1,4-cholestadien-3-one (III). A mixture of 3.0 g. of 1,4-cholestadien-3-one (I, R = C_8H_{17}), 1.41 g. of N-bromosuccinimide, 0.1 g. of benzoyl peroxide and 80 cc. of car-

[1] All melting points are corrected and were determined on the Kofler block. Rotations were carried out on 60–100 mg. of substance in 10 cc. of chloroform in a 2 dm. tube,

bon tetrachloride was refluxed in the presence of strong light (photoflood lamp) until all the succinimide had risen to the surface of the solution (*ca.* forty minutes). After filtration and evaporation *in vacuo*, the residue was crystallized from ether-methanol yielding 2.2 g. (61%) of the 6-bromo derivative III. The analytical sample was obtained as colorless needles from ether-methanol, m.p. 142–144°, $[\alpha]_D^{20}$ +30.6°, u.v. maximum at 250 mμ (log E 4.24); lit. (5): 47% yield, m.p. 144–145°, u.v. max. at 248 mμ.

Anal. Calc'd for $C_{27}H_{39}BrO$: C, 70.55; H, 8.55.
Found: C, 70.62; H, 8.79.



a. R = C_8H_{17}; R′ = H
b. R = C_8H_{17}; R′ = C_6H_5CO
c. R = C_8H_{17}; R′ = 3,5-$(NO_2)_2C_6H_3CO$

a. R = C_8H_{17}; R′ = H
b. R = C_8H_{17}; R′ = CH_3CO
c. R = C_8H_{17}; R′ = CH_3

a. R = H
b. R = *p*-$NO_2C_6H_4CO$

1,4,6-Cholestatrien-3-one (*IV*, *R* = C_8H_{17}). The dehydrobromination was accomplished by refluxing 0.7 g. of the 6-bromo derivative III with 3 cc. of collidine for fifteen minutes,

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while all spectra were taken in 95% ethanol solution. We are indebted to the Srtas. Ann Rochmann and Paquita Revaque for these determinations and to Srta. Amparo Barba of our Microanalytical Department and Mr. Joseph F. Alicino, Metuchen, New Jersey for the microanalyses. The alumina used in all chromatograms was obtained from the Aluminum Company of America, grade F-20, minus 80-mesh.

which resulted in the formation of 95% of the theoretical amount of collidine hydrobromide. The usual work-up afforded 300 mg. (52%) of cholestatrienone with m.p. 75–78°, which was raised on further recrystallization to m.p. 80–81°, undepressed on admixture with another specimen (4), u.v. maxima at 224 (log E 4.09), 256 (log E 4.03) and 300 mμ (log E 4.09). The present procedure affords unequivocal proof for the structure of the trienone IV, but the alternate method (4) is preferable for large scale work.

Dienone-phenol rearrangement of 1,4,6-cholestatrien-3-one. A solution of 5 g. of the above trienone IV (crude material of m.p. 70–80° could be used) and 1.5 g. of *p*-toluenesulfonic acid in 200 cc. of acetic anhydride was heated on the steam-bath for four hours and then poured into water. After twenty minutes, the product was extracted with ether, washed free of acid, and the solvent evaporated. The residue was purified by filtering a hexane solution through a column of alumina (50 g.) and recrystallizing from ether-hexane; yield, 4.5 g. (81%), m.p. 105–107°. The analytical sample of *1-methyl-3-aceloxy-19-nor-1,3,5,6-cholestatetraene* (*Vb*) had m.p. 112–114° $[\alpha]_D^{20}$ −99.6°, u.v. maxima at 224 (log E 4.42) and 266 mμ (log E 3.94).

Anal. Calc'd for $C_{29}H_{42}O_2$: C, 82.41; H, 10.01.
Found: C, 82.68; H, 9.91.

Saponification with boiling 1% methanolic alkali followed by several recrystallizations from hexane afforded the *free phenol Va* with m.p. 144–146°, $[\alpha]_D^{20}$ −131°, u.v. spectrum Fig. 1.

Anal. Calc'd for $C_{24}H_{40}O$: C, 85.20; H, 10.59.
Found: C, 85.33; H, 10.22.

The *methyl ether Vc* was prepared in the usual manner (8) with dimethyl sulfate and crystallized as colorless prims from ether-methanol, m.p. 64–65°, $[\alpha]_D^{20}$ −115.3°.

Anal. Calc'd for $C_{28}H_{42}O$: C, 85.21; H, 10.72.
Found: C, 85.01; H, 10.92.

1-Methyl-3-hydroxy-19-nor-1,3,5-cholestatriene (*IIa*). One and one-half grams of the 6-dehydro acetate Vb was hydrogenated in 100 cc. of ethyl acetate with 150 mg. of palladium-on-barium sulfate catalyst (American Platinum Works, Newark, N. J.) at room temperature and atmospheric pressure. The oily product was saponified with 2% methanolic potassium hydroxide and the *phenol* IIa was purified by passage through a short column of alumina and crystallization from pentane; yield, 900 mg., m.p. 126.5–128°, $[\alpha]_D^{20}$ +135.6°, u.v. spectrum Fig. 1. The so-called "sterinphenol," previously believed (2) to have this structure melts at 145–146° (2, 8), $[\alpha]_D^{20}$ +161° (8).

Anal. Calc'd for $C_{27}H_{42}O$: C, 84.75; H, 11.06.
Found: C, 84.70; H, 11.27.

The *3,5-dinitrobenzoate* IIc showed m.p. 105–107°, $[\alpha]_D^{20}$ +98.9°, after recrystallization from methanol-ethyl acetate, while the corresponding derivative of Inhoffen's "sterinphenol" melted at 179–180° (2).

Anal. Calc'd for $C_{34}H_{44}N_2O_6$: C, 70.80; H, 7.69.
Found: C, 71.08; H, 7.94.

The *benzoate IIb*, prepared with benzoyl chloride and pyridine, crystallized as needles from acetone-methanol, m.p. 136–138°, $[\alpha]_D^{20}$ +117°.

Anal. Calc'd for $C_{34}H_{46}O_2$: C, 83.89; H, 9.52.
Found: C, 83.90; H, 9.66.

1-Methyl-3-hydroxy-19-nor-1,3,5,6,8-cholestapentaene (*VIa*). After refluxing a solution of 1.5 g. of the acetate Vb in 50 cc. of glacial acetic acid with 0.25 g. of freshly sublimed selenium dioxide for thirty minutes, water was added, the product was extracted with ether, washed with sodium carbonate solution and evaporated. The residue (1.3 g.) was saponified by boiling for thirty minutes with 1% methanolic potassium hydroxide solution, yielding 0.9 g. of an oil, which on chromatographing over 20 g. of alumina afforded 0.7 g. of yellowish oil. Treatment with a saturated ethanol solution of picric acid led to 0.6 g. of a red picrate, m.p. 148–149°. Five hundred milligrams of the picrate was decomposed by partitioning between ether and dilute ammonium hydroxide solution and the phenol, thus regenerated, was crystallized from pentane leading to pale yellow crystals of the phenol

VIa (0.3 g.) with m.p. 154–155°, $[\alpha]_D^{20}$ +47.7°. The substance rapidly turned brownish on exposure to light and air. Its ultraviolet absorption spectrum is depicted in Fig. 1 and though clearly demonstrating the presence of the naphthol moiety, differs somewhat from that of 1-methylequilenin (3), possibly due to the lability of the substance.

Anal. Calc'd for $C_{27}H_{38}O$: C, 85.65; H, 10.11.
Found: C, 85.34; H, 9.96.

The *p-nitrobenzoate VIb* was prepared by heating 100 mg. of the above phenol (VIa) for fifteen minutes with 2 cc. of pyridine and 500 mg. of freshly prepared *p*-nitrobenzoyl chloride, and after recrystallization from chloroform-methanol was obtained as yellowish needles with m.p. 146–148°, $[\alpha]_D^{20}$ +38.7°.

Anal. Calc'd for $C_{34}H_{41}NO_4$: C, 77.38; H, 7.83.
Found: C, 77.49; H, 8.03.

SUMMARY

1,4,6-Cholestatrien-3-one (IV), prepared by two independent methods, was subjected to the dienone-phenol rearrangement yielding a 1-methyl-6-dehydro phenol (V), which on hydrogenation produced the authentic 1-methyl-3-hydroxy-1,3,5-triene II of the cholesterol series. This product proved to be different from Inhoffen's "sterinphenol" obtained by dienone-phenol rearrangement of 1,4-cholestadien-3-one (I) and thus affords further proof that the dienone-phenol rearrangement in the steroid series proceeds in a different manner in the presence of an additional conjugated double bond. Dehydrogenation of the 6-dehydro derivative Vb with selenium dioxide led to the first naphthalenic analog in the cholesterol series.

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